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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,200	LYNCH ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 8 12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's arguments filed 5-10-03, paper number 10, have been fully considered but they are not persuasive. The declaration by Dr. Geary file 5-10-03, paper number 9, has been considered but is not persuasive. The declaration by Dr. Lynch file 5-28-03, paper number 11 has been considered but is not persuasive.

Claims 7, 15 and 16 have been canceled. Claims 1-6 and 8-14 are pending and under consideration in the instant application.

The IDS filed 9-6-02, paper number 6, the IDS filed 3-10-03, paper number 8, and the IDS filed 4-28-03, paper number 12, have been entered. Reference 14 in the IDS filed 9-6-02 has not been considered because a copy has not been provided. Reference 1 in the IDS filed 5-10-03 has not been considered because a translation has not been provided.

Claim Objections

Claims 2-6 and 8-14 should begin --The method according to claim...--. Use of "A method..." when reference one parent claim is improper.

Claim Rejections - 35 USC § 112

Claims 1-6 and 8-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims as amended are new matter because the specification does not contemplating a "sufficient dosage and for a

sufficient duration to transduce said cells" or merely making "a product of the nucleic acid of the rAAV". Applicants point to pg 8, lines 24-28, pg 19, lines 22-32 and Examples 2-7 which do not teach the limitations claimed. Pg 8 contemplates transducing cells. Pg 19 contemplates how the AAV is delivered *in vivo* and is not limited to blood vessels.

Claims 1-6 and 8-14 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising administering an AAV vector comprising a nucleotide sequence encoding a marker protein operatively linked to a promoter into an artery following balloon catheter injury such that expression of the marker protein occurs in adventitial, microvascular endothelial cells, does not reasonably provide enablement for merely introducing an AAV vector into a blood vessel, introducing an AAV vector comprising a therapeutic gene, treating an individual by transducing a cell with an AAV vector encoding a therapeutic gene, introducing an AAV vector into a microvessel or into the adventitia of an artery without using a balloon catheter, or transducing microvascular cells without using a balloon catheter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Claim 1 is directed toward transducing cells of a blood vessel *in vivo* by contacting said cell with an AAV vector. Claim 14 requires the AAV vector is introduced into the adventitia of an artery. None of the claims require expression of a protein encoded by the AAV vector. Mere introduction of an AAV into a blood vessel or cell

does not have a use that is enabled in the specification or the art at the time of filing. What is required is expression of the protein. As such the claims should clearly set forth that introducing AAV results in expression of a protein encoded by the AAV. It is noted that for protein expression to occur, the AAV vector must comprise a nucleic acid sequence encoding a protein operably linked to a promoter. The promoter is essential to obtain protein expression because it cannot occur otherwise. For example –A method of expressing a protein *in vivo* comprising introducing a recombinant adeno-associated virus (rAAV) vector into a blood vessel *in vivo,* wherein said rAAV comprises a nucleic acid sequence encoding a protein operably linked to a promoter, resulting in expression of said protein to detectable levels *in vivo*.—

Claim 1 is directed toward transducing cells of a blood vessel *in vivo* by introducing an AAV vector into a blood vessel. Dependent claims require the blood vessel is a microvessel (claims 5, 6), the cell is a microvascular cell (claims 11-13) or introducing the vector into the adventitia (claim 14). The specification teaches injecting AAV into blood vessels following balloon catheter injury resulted in expression in microvessels, microvascular cells or the adventitia (pg 31, Example 4; pg 32, line 25). The specification teaches injecting AAV into blood vessels without using balloon catheter injury did not result in expression in microvessels, microvascular cells or the adventitia (pg 32, line 27, "control artery"; pg 29, Example 3; pg 31, line 16). Lynch (1997, Circulation Res., Vol. 80, pg 497-505) confirmed that expression was "found only in the adventitia of one of the two denuded common carotid arteries (pg 501, col. 2, 8 lines from the bottom). The art at the time of filing did not teach obtaining expression in

microvessels, microvascular cells or the adventitia by injecting AAV into a blood vessel without a balloon catheter. Given the teachings in the art taken with the guidance in the specification it would require one of skill undue experimentation to determine how to obtain delivery or expression in microvessels, microvascular cells or the adventitia without a balloon catheter as broadly encompassed by the claims.

Claim 4 requires the AAV vector comprises a therapeutic gene. Claim 4 does not require obtaining any therapeutic effect. The only purpose of administering AAV vectors comprising therapeutic genes is for obtaining a therapeutic effect (pg 2, line 13; pg 7, line 21). Mere introduction of an AAV comprising a therapeutic gene into a blood vessel or cell as claimed does not have a use that is enabled in the specification or the art at the time of filing.

Furthermore, the specification does not enable one of skill to use the claimed invention to obtain a therapeutic effect. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering

successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art, which show promise, but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Thus, it was unpredictable what combination of elements were required to obtain a therapeutic effect using gene therapy by introducing AAV encoding a therapeutic gene into the blood vessel.

The specification teaches administering AAV vectors encoding marker proteins to the adventitial microvessels of an artery in a cholesterol fed monkey model (Examples 3-7; pages 29-37). The specification contemplates delivering therapeutic genes to treat atherosclerosis (page 21, line 16). The specification does not teach the amount of protein expression required to obtain a therapeutic effect, the target cells of the blood

vessel required to obtain the desired effect or the effect of expression in cells of microvessels. The specification does not teach obtaining a therapeutic effect by introducing AAV into a blood vessel. Nor did the art at the time of filing teach administering AAV into a blood vessel caused a therapeutic effect. Given the state of the art at the time of filing taken with the teachings in the specification and the lack of correlation between marker proteins and therapeutic proteins, the lack of guidance regarding the parameters required to target the desired tissue and obtain a therapeutic effect, and the breadth of the claims, it would have required one of skill in the art at the time the invention was made undue experimentation to determine the parameters required to obtain a therapeutic effect by introducing an AAV encoding a therapeutic protein into a blood vessel.

Applicants argue expression of protein is not required for the claimed method to be useful because obtaining RNA is useful. Applicants cite the specification, which contemplates forming ribozymes or antisense RNA. Applicants' argument is not persuasive. None of the claims require formation of ribozymes or antisense. In fact, claims 2-4 must result in protein expression because the AAV comprises a detectable marker, selectable marker or a therapeutic gene, which are all proteins that must be expressed. The specification does not enable using ribozymes or antisense by teaching how to obtain functional ribozymes or antisense *in vivo* that cause a therapeutic effect, the only disclosed use for ribozymes or antisense.

Applicants' arguments regarding a declaration by Dr. Geary filed August 17, 1999 are moot because the declaration has not been filed in the instant application. The

argument does not state the methods used in the declaration are those disclosed in the instant application.

Applicants' arguments regarding obtaining a therapeutic effect are not persuasive. The declaration by Dr. Carter has not been filed in the instant application. The examiner has provided references that establish the unpredictability of obtaining a therapeutic effect using gene therapy. In other words, it was not known how to obtain therapeutic levels of expression of a protein *in vivo* using AAV gene therapy at the time of filing. Applicants have not overcome the unpredictability in the art at the time of filing by teaching one of skill how to obtain therapeutic levels of expression of a protein in a cell of a blood vessel using the claimed method. No affidavit as to the examiner's personal knowledge is required. The examiner need not provide evidence that AAV could not provide therapeutic levels of expression; the examiner need only establish that the art at the time of filing did not teach how to obtain therapeutic levels of expression *in vivo* using AAV.

I. Claims 1-6 and 8-14 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 and 8-14 remain indefinite because the claims do not clearly set forth the steps of the method. Merely contacting cells with an AAV "to transduce said cells" does not clearly set forth that the AAV is injected into a blood vessel *in vivo* resulting in transduction of cells. As written "at a sufficient dosage and for a sufficient duration to

transduce said cell" is confusing and reads as an intended use, which may not occur. Describing the dosage and duration of how the AAV contacts the cells is confusing. The claims should result in transduction of cells. In addition, merely making a product of the nucleic acid of the AAV is unclear. Is the claim limited to a "product" that is exogenous to the AAV, or does the claim encompass making AAV "products" such as viral coat proteins?

Claim Rejections - 35 USC § 102

II. Claims 1-6 and 8-14 remain rejected under 35 U.S.C. 102(e) as being anticipated by Kaplitt (US Patent 6,162,796, Dec. 19, 2000) for reasons of record.

Kaplitt administered an AAV vector encoding lacZ into the mid-circumflex coronary artery using a catheter and obtained expression in the heart (col 14, lines 33-51, Fig. 1-3, col. 5, line 61 through col. 6, line 1). Kaplitt delivered an AAV vector encoding various proteins and expressed the protein in various "target cells," including vascular endothelial cell and human cells (see claims 1, 9, 23 and 24). Kaplitt transduced the cells of the blood vessel because protein was expressed in various "target cells." Claim 10 is included because the target cells of Kaplitt are inherently proliferating because all cells regenerate. Thus, Kaplitt anticipates the claims.

Applicants argue the date of the claimed invention was prior to September 27, 1995 (the filing date of Kaplitt). Applicants provide a declaration by Dr. Geary stating the claimed invention was completed prior to Sept. 27, 1995. Applicants' argument is not persuasive. Prior invention may not be established using a declaration if the

rejection is based upon a U.S. patent to another which claims the same patentable invention MPEP 715 [R-1]. Claim 26 of '796 is directed to delivering AAV to a peripheral artery *in vivo* and obtaining transduction of cells and expression of a protein encoded by AAV, which is equivalent to claim 1 in the instant application, which requires contacting cells with AAV *in vivo* such that the cell is transduced and a product of the AAV is made. Furthermore, the declaration itself is not persuasive. The dates Exhibits A-E were prepared have been blacked out on all the documents; therefore, the date of invention cannot be established as being prior to September 27, 1995. Exhibits A-C do not describe obtaining transduction of cells or expression of proteins *in vivo*. Exhibit D does not mention AAV, transduction of cells, expression of a protein or that the AAV was administered *in vivo*. Exhibit E does not mention AAV, administration of AAV *in vivo* or that any cells expressed a protein after staining. Therefore, the declaration does not establish that the claimed invention was obtained or that the work done was prior to September 27, 1995.

III. Claims 1-6 and 8-13 remain rejected under 35 U.S.C. 102(e) as being anticipated by Podsakoff (US Patent 5,858,351, Jan. 12, 1999) for reasons of record.

Podsakoff taught delivering a recombinant AAV vector encoding EPO operatively linked to a promoter into the tail vein of mice and obtaining detectable expression of EPO in the serum (col. 20, lines 1-20; col. 22, lines 8-19; Fig. 7). Claim 10 is also included because the cells that express EPO are inherently proliferating. Podsakoff also taught transducing myocytes of the heart by injecting AAV into the left ventricular apex of the heart (col. 22, lines 41-52). Injecting AAV into the left ventricular apex of the

heart is equivalent to introducing AAV into a blood vessel as claimed because the heart is a vessel containing blood. The myocytes expressing beta-gal are inherently proliferating.

Applicants argue the date of the claimed invention was prior to Jan. 18, 1996 (the filing date of Podsakoff) and provides a declaration by Dr. Geary stating the claimed invention was completed prior to Sept. 27, 1995. Applicants' argument is not persuasive. Prior invention may not be established using a declaration if the rejection is based upon a U.S. patent to another which claims the same patentable invention MPEP 715 [R-1]. Claim 4 of '351 is directed to delivering AAV to cardiac muscle cells *in vivo* and obtaining expression of a protein encoded by AAV, which is equivalent to claim 1 in the instant application, which requires contacting cells with AAV *in vivo* such that the cell is transduced and a product of the AAV is made. Furthermore, the declaration itself is not persuasive. The dates Exhibits A-E were prepared have been blacked out on all the documents; therefore, the date of invention cannot be established as being prior to September 27, 1995. Exhibits A-C do not describe obtaining transduction of cells or expression of proteins *in vivo*. Exhibit D does not mention AAV, transduction of cells, expression of a protein or that the AAV was administered *in vivo*. Exhibit E does not mention AAV, administration of AAV *in vivo* or that any cells expressed a protein after staining. Therefore, the declaration does not establish that the claimed invention was obtained or that the work done was prior to September 27, 1995.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 and 8-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Bahou (1994, State Univ. of NY, Grant Number HL-94-007-B).

Bahou taught data showing detection of AAV encoding lacZ gene products upon contacting AAV encoding lacZ with cells of a blood vessel *in vivo*. Thus, Bahou anticipates the claims. Claims 2-4 are included because the selectable and detectable markers and therapeutic genes are intended uses and are not required to occur. In addition, lacZ gene products were detected.

Claim Rejections - 35 USC § 103

The rejection of claims 1-6 and 8-14 under 35 U.S.C. 103(a) as being unpatentable over Branellec (US Patent 5,851,521, Dec. 22, 1998), as supported by Nabel (5,328,470, July 12, 1994) has been withdrawn.

The rejection of claims 1-6 and 8-14 under 35 U.S.C. 103(a) as being unpatentable over Branellec (US Patent 5,851,521, Dec. 22, 1998) in view of Kaplitt (US Patent 6,162,796, Dec. 19, 2000), as supported by Nabel (5,328,470, July 12, 1994) has been withdrawn.

Applicants argue Branellec is not a valid reference because is does not qualify as a reference under 102(a). Specifically, applicants argue the issue date of Branellec (Dec. 22, 1998) is not "before the invention thereof by the applicant for patent" as required in 102(a). Applicants' argument is correct but not for the reasons cited. 102(a)

requires: (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. Branellec is not a valid reference because Branellec did not describe transducing cells of a blood vessel *in vivo* with AAV in the US until March 29, 1996, or in France until March 31, 1995, which is after the effective filing date of the instant application, March 3, 1996.

Double Patenting

The rejection of claim 11 under 37 CFR 1.75 as being a substantial duplicate of claim 7 has been withdrawn because claim 7 has been canceled.

Conclusion

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 3-10-03 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER